# Medical Staff Conference

## Current Concepts in Bacterial Meningitis

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*These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Homer A. Boushey, MD, Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.*

MERLE A. SANDE, MD*: *Bacterial meningitis remains a devastating infection, with a high incidence of attendant morbidity and mortality, especially in patients at the extremes of age. New antibiotics have done little to change this. Much has been learned in the past 10 to 15 years, however, about the pathophysiology of this disease, and new avenues for therapeutic intervention have been opened. Stephen M. Hahn, MD, has reviewed these studies and puts them in clinical perspective in this Medical Staff Conference.*

STEPHEN M. HAHN, MD†: Many advances have been made since the early part of this century in the diagnosis and treatment of bacterial meningitis. The introduction of antibiotics led to a dramatic decrease in morbidity and mortality. Notable advances have not occurred, however, since the introduction of antibiotics; residual morbidity and mortality are still unacceptably high. New methods of therapy beyond the development of antibiotics are required.

### Etiology and Epidemiology

*Streptococcus pneumoniae, Hemophilus influenzae,* and *Neisseria meningitidis* account for more than 80% of the cases of meningitis in adults in the United States.[1,2] *Listeria monocytogenes* and gram-negative organisms cause most of the other 20% of cases. Meningitis is more common in children, with 75% of all cases reported to the Centers of Disease Control in 1978 occurring in patients younger than 5 years.[3] In the neonatal age group (younger than 1 month) group B *Streptococcus* and *Escherichia coli* are the major pathogens. In children older than 1 year and younger than 5 years, *H influenzae* accounts for the majority of cases. Of the three major pathogens in adults, *H influenzae* accounts for about 5% of the cases, *N meningitidis* accounts for 25% to 40%, and *S pneumoniae* accounts for 40% to 50%.[1] Case-fatality rates vary depending on the specific pathogen involved. Most series report the highest case-fatality rate with pneumococcal meningitis. Data from the National Bacterial Meningitis Surveillance Study showed a case-fatality rate of 26% for pneumococcal meningitis, 6% for *H influenzae,* and 10% for *N meningitidis* (Table 1).[2] Overall, in most series, the case-fatality rate for bacterial meningitis is about 10% to 20%.

### Diagnosis

The diagnosis of bacterial meningitis is based on recognizing the appropriate clinical features. Two different presentations have been described.[4,5] The first is progressive illness that occurs over a 12- to 24-hour period. Nonspecific signs of fever, malaise, and myalgias occur several days before admission. In the second mode of presentation, the tempo is much quicker and signs and symptoms of meningitis develop over a few hours. Some authors have postulated that a higher bacterial load exists in the patients with the more rapid onset of the disease and claim that a worse prognosis results.

The most important symptoms seen on presentation include fever, chills, sweats, myalgias, confusion, headache, nausea, vomiting, and photophobia. Signs include nuchal rigidity, Brudzinski's and Kernig's signs, fever, and an altered mental state (Table 2). Physicians must not be fooled by a lack of classic signs and symptoms. Some patients with meningitis, especially the elderly and very young, will present with subtle mental state changes and no fever.

Patients with pneumococcal and *H influenzae* meningitis will often have an associated suppurative focus. Otitis media or mastoiditis is seen in 30%, pneumonia in 25%, sinusitis in 10% to 15%, and endocarditis in 5% of patients with pneumococcal meningitis.

The cerebrospinal fluid (CSF) findings are variable. The CSF leukocyte count is usually between 1,000 and 5,000 $\times$ $10^6$ per liter (1,000 and 5,000 per $\mu$l), although the count may be as low as a few cells or as high as 10,000. Cerebrospinal fluid leukocyte counts nearing 10,000 $\times$ $10^6$ per liter should alert a clinician to the possibility of a brain abscess that has ruptured into the subarachnoid space. Polymorphonuclear cells usually account for about 80% of the leukocytes. In patients with *L monocytogenes* meningitis, mononuclear cells may predominate. The CSF glucose level is usually less than 2.2 mmol per liter (40 mg per dl) or less than 50% of the peripheral glucose value. The CSF protein value is usually between 1.0 and 5.0 grams per liter (100 and 500 mg per dl), although levels higher than 10.0 grams per liter (1,000 mg per dl) have been reported.

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(Hahn SM: Current concepts in bacterial meningitis [Medical Staff Conference]. West J Med 1989 Aug; 151:180-186)

ABBREVIATIONS USED IN TEXT
CIE = counterimmunoelectrophoresis
CSF = cerebrospinal fluid

The diagnosis of bacterial meningitis is established by identifying organisms on a Gram's stain or culture of the CSF. In most series, the Gram's stain shows an organism in 70% to 80% of all cases not previously treated with antibiotics. The CSF culture is also positive for organisms in about 80% of all cases.[1,4,5] Administering antibiotics before the lumbar puncture does not change the CSF cell counts or chemistry values but may cause a significant reduction in the diagnostic value of Gram's stains and CSF cultures. Blood cultures are positive for meningitis organisms 40% to 90% of the time.[5,6]

The diagnosis of bacterial meningitis in patients who have previously taken antibiotics has been augmented with the introduction of tests that measure bacterial antigens, the counterimmunoelectrophoresis (CIE) and latex agglutination tests. These tests are no more sensitive or specific than a Gram's stain and culture in patients who have not previously taken antibiotics. The CIE test is available for pneumococci (83 serotypes), *H influenzae* (type b), and meningococci (serogroups A or C). There is no CIE test available for the most common meningococcus that causes meningitis, group B. The sensitivity of the test depends on the specific pathogen involved and varies from 50% to 90%.[1,5] Cross reactions do occur but are relatively uncommon when the test is done properly. The latex agglutination test is more sensitive than the CIE and is less expensive and easier to do.

TABLE 1.—*Bacterial Meningitis Cases and Fatality Rates—The National Bacterial Meningitis Surveillance Study, N=13,974**

| Pathogen | Patients No. | Patients % | Fatality Rate, % |
|---|---|---|---|
| *Hemophilus influenzae* | 6,756 | 48.3 | 6.0 |
| *Neisseria meningitidis* | 2,742 | 19.6 | 10.3 |
| *Streptococcus pneumoniae* | 1,865 | 13.3 | 26.3 |

*Adapted from Schlech et al.[2]

TABLE 2.—*Symptoms and Signs in Bacterial Meningitis**

| Finding | Relative Frequency, % |
|---|---|
| Fever | ≥ 90 |
| Headache | 80-90 |
| Stiff neck | ≥ 80 |
| Brudzinski's sign | 50 |
| Kernig's sign | 50 |
| Myalgia | 30-60 |
| Nausea, vomiting | ≥ 80 |
| Altered sensorium | ≥ 80 |
| Cranial nerve palsy | 10-15 |
| Seizures | 20-30 |
| Focal cerebral signs | 10-15 |
| Papilledema | < 5 |
| Suppurative foci | 0-30 |

*From Scheld.[1]

TABLE 3.—*A Retrospective Review of 349 Cases of Acute Bacterial Meningitis Over a 25-Year Period*†*

| Change | Total Cases | Deaths, % |
|---|---|---|
| Mild | 111 | 10 |
| Moderate | 118 | 22 |
| Severe | 118 | 45 |

*Adapted from Hodges and Perkins.[9]
†$P<.01$.

## Sequelae of Bacterial Meningitis

The sequelae of bacterial meningitis are largely neurologic. Global cerebral dysfunction, ranging from simple irritability to confusion, delirium, lethargy, and coma, is most common at presentation. Permanent cerebral dysfunction is a possible sequela. Seizures are most often seen in the pediatric population and occur in about 30% of cases.[1,5] Generalized seizures are not felt to be a poor prognostic sign, especially early in the disease. Focal seizures, however, should suggest the presence of more significant disease. Focal neurologic signs may appear early or late in the course. In early meningitis, focal neurologic abnormalities are a clue to the presence of a brain abscess, Todd's paralysis (after a seizure), or vasculitis with infarction. If focal abnormalities appear late in the course, a more serious disorder is implied, including subdural empyema or effusion, venous thrombophlebitis, abscess, hemorrhage, or infarction. A well-recognized complication of meningitis is cortical vein thrombosis; this occurs ten days to two weeks after the onset of meningitis and results in a strokelike syndrome.[4] Finally, cranial nerve abnormalities accompany meningitis in about 10% to 20% of cases.[1] The eighth cranial nerve complex is often involved, resulting in deafness and ataxia. In one prospective study of children with bacterial meningitis, 10% of the patients had permanent unilateral or bilateral sensorineural hearing impairment. Another 16% had transient conductive hearing abnormalities.[7] Abnormalities of cranial nerves III, IV, and VI also occur, often in patients with increased intracranial pressures. Neurologic sequelae are estimated to be present in about 20% of patients with bacterial meningitis. The highest rates are seen in infants and neonates and with pneumococcal meningitis.

One retrospective study has attempted to assess the subjective outcome of meningitis.[8] Patients were contacted several years after an episode of bacterial meningitis and given a questionnaire asking about residual symptoms. There was no matched control group. Of the respondents, 38% reported residual symptoms including chronic headaches, an inability to concentrate, loss of memory, impaired hearing, visual changes, dizziness, and an impaired ability to function in work or school.

## Prognostic Factors

Two important prognostic factors emerge from the literature: the age of the patient and the level of consciousness on admission. Not surprisingly, patients older than 60 years or younger than 1 year have the worst prognosis. Patients who present with substantially reduced consciousness also have the worst prognosis (Table 3).[9] In one prospective study of meningitis, 33% of children who presented with irritability, lethargy, or somnolence were found to have abnormalities on a neurologic examination on discharge.[10(p293)] Of those comatose or semicomatose on admission, 53% had neurologic abnormalities on discharge. In another review of 1,316 cases of meningitis, a significant correlation was found between

TABLE 4.—*Guidelines for Initial and Alternative Antibiotic Regimens in the Treatment of Adult Bacterial Meningitis*

| Pathogen | Initial Choice | Alternative |
|---|---|---|
| *Streptococcus pneumoniae*<br>*Neisseria meningitidis* | Penicillin G | 3rd-generation cephalosporin*; cefuroxime; chloramphenicol† |
| *Hemophilus influenzae* | Cefuroxime; 3rd-generation cephalosporin*; chloramphenicol† | Trimethoprim-sulfamethoxazole; ampicillin‡ |
| *Listeria monocytogenes* | Ampicillin | Penicillin G; ? trimethoprim-sulfamethoxazole; ? chloramphenicol† |
| Gram-negative organisms | 3rd-generation cephalosporin* | |

*Third-generation cephalosporins should be considered in the following order: ceftriaxone sodium, cefotaxime sodium, and ceftizoxime sodium.
†The use of chloramphenicol should be considered only in patients with both penicillin and cephalosporin allergies.
‡All antibiotic therapy should be tailored to the results of cultures and sensitivities.

TABLE 5.—*A Model for the Pathogenesis of Bacterial Meningitis**

Attaches to the mucosal cells
Transgresses the mucosal barrier
Survives in the bloodstream
Enters the cerebrospinal fluid
Survives in the cerebrospinal fluid
Causes disease in the meninges and brain

*From McGee.[14]

the level of consciousness on admission and the case-fatality rate.[11]

Cerebrospinal fluid values on admission, including the CSF protein concentration, glucose concentration, and leukocyte count, have not correlated consistently with neurologic sequelae or mortality. The duration of illness before admission and the duration of illness before receiving the first dose of antibiotics have been touted as significant but have not been consistently associated with mortality. Prior antibiotic therapy does interfere with the yield of organisms on a CSF Gram's stain or culture but does not significantly affect the neurologic outcome or mortality. Other important microbiologic criteria, including bacterial antigen levels and the density of bacteria on culture, have been correlated with the prognosis in some studies,[6] but confirmation of these findings is still needed. Associated illnesses, including sickle cell anemia, alcoholism, and diabetes mellitus, worsen the prognosis of bacterial meningitis.

## Treatment

Despite the conflicting data regarding the prognostic importance of the early administration of antibiotics, it is prudent to begin treatment as soon as possible. Bactericidal antibiotics in concentrations that are well above the mean bactericidal concentration are necessary.[12] The use of an antibiotic before doing a lumbar puncture is controversial. There are some data from studies in animals to support the concept that there is a "golden period" of four hours after the administration of antibiotics during which time the yield of a CSF bacterial culture is acceptable. There are yet no data from humans to support or refute this concept. The decision of when to administer antibiotics should be left to the individual clinician. Nonetheless, antibiotics should always be administered after blood specimens are taken for culture.

Antibiotic therapy is based on the clinician's initial reading of the CSF Gram's stain (Table 4). Intravenous penicillin G or ampicillin is still the most appropriate drug of choice for possible meningococcal, pneumococcal, or listerial meningitis. A third-generation cephalosporin, cefuroxime, or chloramphenicol may be considered as appropriate therapy in penicillin-allergic patients with pneumococcal or meningococcal meningitis or for suspected *H influenzae* meningitis. Therapy should always be tailored to the culture results and sensitivities. The appropriate duration of therapy for meningitis in adults has not been extensively studied, although seven to ten days is considered acceptable.

## Pathophysiology

Advances in the understanding of the pathophysiology of bacterial meningitis come largely from studies done in the rabbit pneumococcal meningitis model of Dacey and Sande.[13] These studies have led to an understanding of the inflammatory response to bacterial invasion of the subarachnoid space and of how this is related to neurologic sequelae.

Bacterial meningitis is initiated by one of three mechanisms, a primary bacteremia, direct contiguous spread, or direct entry from trauma. In one model, bacteria attach to a mucosal surface, often the nasopharynx (Table 5).[14] This is followed by movement of the bacteria across the mucosal barrier, their survival in the bloodstream, and seeding of the CSF. Bacterial survival in the bloodstream and CSF depends on their avoiding phagocytosis. The antiphagocytic polysaccharide capsule of the pneumococcus appears to enhance survival.[14] How the bacteria actually cross the blood-brain barrier is unclear. Once they do enter the protected environment of the subarachnoid space, the inflammatory response is initiated and central nervous system tissue damage results.

Changes in the blood-brain barrier occur after the bacteria invade the subarachnoid space. This barrier is thought to be composed of the choroid plexus, the cerebral microvasculature, and the arachnoid membrane.[15,16] It is normally an effective filtering mechanism for the CSF. The capillaries at these sites have tight junctions, unlike the normal fenestrated capillaries elsewhere in the body. In addition, pinocytic vesicles (a common feature of capillaries) are absent and mitochondria are abundant. Infection in the CSF leads to the appearance of pinocytic vesical formation and a separation of tight junctions.[17] This contributes to the entrance of cells and inflammatory exudate into the CSF. Interestingly, only encapsulated organisms cause a separation of the tight junctions.[17]

Host defenses against bacteria within the CSF are limited. In fact, host-defense mechanisms are ineffective in retarding the growth of bacteria in the first 24 hours of experimental pneumococcal meningitis.[18]

There is little or no complement, opsonic, or bactericidal activity present in normal CSF. During acute pneumococcal meningitis in the rabbit model and in humans, only a small rise in complement activity is seen. Only minimal opsonic or bactericidal activity can be measured.[19] Immunoglobulin levels in the CSF do not rise until late in the course of experi-

mental pneumococcal meningitis.[15] The lack of complement activity and specific immunoglobulin are major reasons for the lack of effective host defenses in the CSF. All of these findings suggest that bacterial meningitis represents an infection in the regional area of impaired host resistance.[15]

Twelve hours after infection is initiated in the rabbit model, enhanced chemotactic activity—probably complement-mediated—leads to a CSF leukocytosis.[17] β-Lactam antibiotics may increase the intensity of the inflammatory response by causing lysis of the pneumococcal cell wall. Experimental studies have confirmed that the teichoic acid portion of the pneumococcal cell wall is particularly important in inducing inflammation.[20] The generation of leukocytosis, however, does not appear to be important for host defenses. Ernst and co-workers measured bacterial growth rates and maximal bacterial titers in rabbits rendered leukopenic with the administration of mechlorethamine hydrochloride (nitrogen mustard) and in control rabbits with experimental pneumococcal meningitis (Figure 1).[18] There was no difference in the two groups with respect to bacterial growth rates or maximal bacterial titers. Why the polymorphonuclear cells contribute so little to the control of the infection has not been fully explored. The lack of complement or specific immunoglobulin may be important. In addition, there is evidence that phagocytosis is more efficient in a closed tissue space. The free floating space of the CSF may not allow for sufficient contact for this "surface phagocytosis."[21]

Experimental evidence suggests that the inflammatory response generated in meningitis does not offer protection against invading bacterial organisms. Another line of experimental evidence suggests that it may even be harmful.

The hallmark of bacterial meningitis is the inflammatory exudate within the subarachnoid space. Inflammation causes cerebral edema and increased CSF outflow resistance, which lead to an increased intracranial pressure. Abnormalities in the cerebral blood flow, cerebrovascular autoregulation, and increased CSF lactate levels—a measure of cerebral ischemia—often follow sustained increases in the intracranial pressure.

Cerebral edema is probably the result of both vasogenic and cytotoxic edema. The opening of the capillaries of the blood-brain barrier in response to infection leads to movement of fluid into the interstitium of the brain (vasogenic edema). There is some experimental evidence to suggest that the cytotoxic effects of leukocyte membranes—especially arachidonic acid metabolites—cause edema and direct tissue damage.[22,23] Cerebral edema certainly contributes to increases in the intracranial pressure.

The major compensatory mechanism of the brain to an increased intracranial pressure is the outflow of CSF from the subarachnoid space to the dural venous sinus blood. The CSF outflow resistance is increased in bacterial meningitis, and further increases in the intracranial pressure often occur. Additionally, the removal of potential toxic substances from the CSF is significantly decreased. This is likely from the buildup of inflammatory exudate within the arachnoid villi.[13]

Vasculitis and venulitis commonly accompany bacterial meningitis.[24,25] These vascular changes may have a direct effect on cerebral blood flow and also lead to increases in the intracranial pressure.

The brain exists in a fixed space and has a sophisticated mechanism for controlling its volume to fit this space. Cerebral perfusion pressure is equal to the mean arterial pressure minus the intracranial pressure. As the intracranial pressure increases, the mean arterial pressure must also increase to maintain an adequate cerebral perfusion pressure (a possible explanation for the Cushing's reflex). In experiments conducted by Tureen and associates in the rabbit model, normal autoregulation was determined.[26] Over a wide range of blood pressures, the cerebral blood flow is constant. In infected rabbits, cerebrovascular autoregulation is faulty, leading to a direct effect of the blood pressure on the cerebral blood flow (Figure 2).[26] Tureen and colleagues also showed that as the cerebral blood flow increased, so did the intracranial pressure (Figure 3). To maintain the cerebral perfusion pressure, the mean arterial pressure increases in response to increases in the intracranial pressure. In infected rabbits, this increased arterial pressure leads to direct increases in cerebral blood flow and still further increases in the intracranial pressure. As the intracranial pressure continues to rise, the cerebral

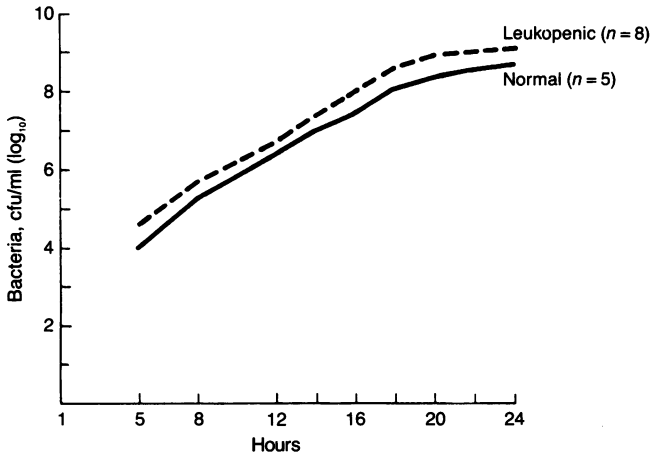


**Figure 1.**—The graph shows the bacterial growth rates in the cerebrospinal fluid of rabbits with experimental pneumococcal meningitis. Bacterial growth rates in rabbits rendered leukopenic with the administration of mechlorethamine hydrochloride are nearly identical to those of control rabbits with normal leukocyte counts. These data suggest that leukocytes contribute little to the initial host defense against bacterial meningitis (from Ernst et al[18]). cfu = colony-forming units

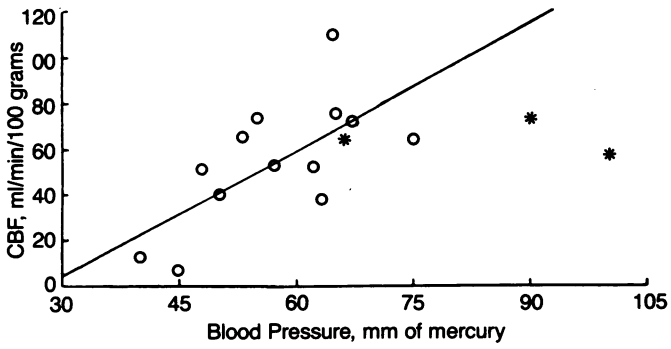


**Figure 2.**—The graph shows the relationship of the cerebral blood flow (CBF) to blood pressure in experimental pneumococcal meningitis in rabbits. In uninfected rabbits (*), the CBF is constant over a wide range of blood pressures, showing normal cerebrovascular autoregulation. Increases in the blood pressure in infected rabbits (o) are associated with an increase in the CBF, consistent with a loss of cerebrovascular autoregulation (from Tureen et al[26]). $r = .63$, $P < .02$

blood flow eventually falls, leading to regional or generalized cerebral ischemia. This has possible implications for the control of the intracranial pressure. Volume depletion has been one mode of therapy used to decrease the intracranial pressure. In the rabbit model, decreases in arterial pressure as a result of volume depletion could result in dangerous decreases in cerebral blood flow and worsening cerebral ischemia.

Some of the data from animals regarding cerebral blood flow have been confirmed in humans. Paulson and coworkers measured the mean hemispheric blood flow in patients with pneumococcal meningitis and found it was decreased by 30% to 40%.[27] In addition, autoregulation of the cerebral blood flow was impaired. Goiten and Tamir looked at children with severe bacterial meningitis and found that decreases in the cerebral perfusion pressure below a certain level correlated with morbidity and mortality.[28]

A proposed schema for the pathophysiology of meningitis is given in Figure 4. The inflammatory response leads to cerebral edema and increased CSF outflow resistance, both of which cause an increased intracranial pressure. Such an increase, accompanied by abnormalities in cerebrovascular autoregulation, may lead to a decrease in the cerebral blood flow, ultimately causing cerebral ischemia and parenchymal damage.

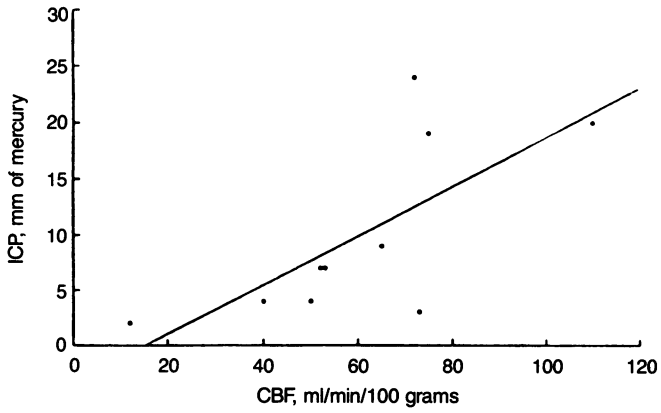


**Figure 3.**—The relationship of the cerebral blood flow (CBF) to the intracranial pressure (ICP) is shown in infected animals. Increases in the CBF lead to direct increases in the ICP (from Tureen et al[26]). $r = .71$, $P < .06$

## Future Therapy

What are the therapeutic implications of the recent developments in the understanding of the pathophysiology of bacterial meningitis? Will interventions that decrease the host inflammatory response lead to decreases in the intracranial pressure and the maintenance of an adequate cerebral blood flow? Will these interventions lead, in turn, to an improved outcome? These questions have only been partially addressed.

Corticosteroids are anti-inflammatory agents used extensively in patients with cerebral edema and increased intracranial pressure. It is postulated that corticosteroids decrease the inflammatory response to bacterial cell wall products, decrease cerebral edema, and decrease outflow resistance in patients with meningitis. This theoretically should lead to the

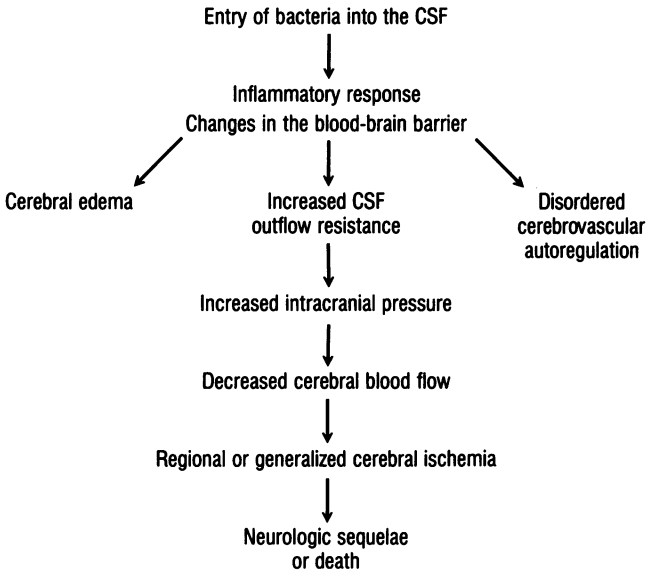


**Figure 4.**—This schema is proposed for the pathophysiology of bacterial meningitis.

TABLE 6.—*Influence of the Administration of Methylprednisolone Sodium Succinate (2 Doses at 30 mg/kg of Body Weight) and of Dexamethasone (2 Doses at 1 mg/kg of Body Weight) on Manifestations of a 24-Hour Infection With Pneumococci in Rabbits*

| | Mean Results ± Standard Deviation* | | | | |
|---|---|---|---|---|---|
| *Treatment* | *Bacterial Titers, log cfu/ml* | *Leukocytes, $\times 10^3$/liter ($10^3/\mu l$)* | *CSF Lactate, mmol/liter (mg/dl)* | *Change in CSF Pressure, mm of mercury* | *Brain Water, grams $H_2O$/100 grams dry wt* |
| No infection† | ND *(11)* | <0.01 *(11)* | 1.6± 0.3 (14.0± 2.6) *(11)* | +0.8±1.4 *(11)* | 396±14 *(11)* |
| 24-hour infection | | | | | |
| No treatment | 7.0±1.2 *(36)* | 2.5±6.6 *(27)* | 8.4± 2.8 (75.3±25.0) *(18)* | +7.5±6.5 *(19)* | 410±11 *(37)*‡ |
| Methylprednisolone | 7.6±0.7 *(14)*§ | 3.9±4.9 *(13)* | 7.1± 3.7 (64.3±33.1) *(13)* | +7.8±5.4 *(13)* | 395± 9 *(14)* |
| Dexamethasone | 6.7±0.6 *(13)* | 2.1±2.2 *(13)* | 4.9± 1.4 (43.8±12.3) *(13)*‖ | +1.8±2.7 *(13)*# | 399±12 *(13)* |

cfu=colony-forming units, CSF=cerebrospinal fluid, ND=not determined

*The italicized numbers in parentheses represent the number of animals tested.
†Pooled data are from 7 animals treated with methylprednisolone and 4 animals treated with dexamethasone.
‡$P < .02$ in comparison with other groups.
§$P < .05$ in comparison with dexamethasone-treated group.
‖$P < .01$ in comparison with untreated infected animals.
#$P < .02$ in comparison with other groups infected for 24 hours.

TABLE 7.—*Two Prospective, Double-Blind, Placebo-Controlled Trials of Dexamethasone in Infants and Children With Bacterial Meningitis**

| End Point | Placebo | Dexamethasone | P Value |
|---|---|---|---|
| Death | 1 | 0 | NS |
| Moderate to severe hearing loss | 13 | 3 | <.01 |
| Requires hearing aid | 12 | 1 | <.001 |

*Adapted from McGee.[14]

maintenance of an adequate cerebral blood flow, a reduction in cerebral ischemia, and less morbidity and mortality. The evidence that corticosteroid use has some of these beneficial effects is just beginning to unfold.

Scheld and associates have shown that penicillin G therapy in rabbits with meningitis did not change the increased resistance to CSF outflow seen, whereas the addition of methylprednisolone decreased both the CSF outflow resistance and the intracranial pressure.[29] Studies by Tauber and colleagues in the same model showed that ampicillin therapy sterilized the CSF and decreased the brain water content, but did not decrease the intracranial pressure.[30] The use of methylprednisolone decreased the brain water content but did not reduce the intracranial pressure. Only the use of dexamethasone substantially decreased the brain water content, the intracranial pressure, and CSF lactate levels (Table 6). Syrogiannopoulos and co-workers showed in an experimental *H influenzae* meningitis model that the use of dexamethasone also decreased brain edema, intracranial pressure, and CSF lactate levels.[31]

Uncontrolled trials and anecdotal reports of corticosteroid therapy in humans with meningitis over the past 20 to 30 years have suggested beneficial effects. Two prospective trials using corticosteroids in patients with meningitis were carried out in the 1960s. DeLemos and Haggerty evaluated the use of methylprednisolone in a randomized placebo-controlled trial of 117 children with bacterial meningitis.[32] No differences between the two treatment groups were seen with respect to neurologic sequelae or mortality. Belsey and associates conducted a randomized placebo-controlled trial of the use of dexamethasone in children with bacterial meningitis.[33] They found a larger incidence of neurologic sequelae in the placebo-treated group. The authors discounted their results, however, because they felt that the placebo group contained more patients with poor prognostic factors. Some of these factors have not been found to correlate significantly with the prognosis.

Lebel and colleagues recently reported two prospective, randomized, placebo-controlled trials of dexamethasone therapy in 200 infants and children with meningitis (Table 7).[34] There was no difference in mortality. Moderate to severe bilateral sensorineural hearing loss and the requirement for hearing aids were substantially reduced in the steroid-treated group. These results are promising. Gastrointestinal bleeding of an unclear cause occurred in two patients treated with dexamethasone. Adverse side effects of dexamethasone use were not otherwise noted. Theoretic concerns remain. A persistence of pneumococci in the CSF well into the course of therapy has been reported in children with meningitis who received corticosteroids.[35] Further trials examining the safety and efficacy of corticosteroid therapy will be necessary in adults.

It is difficult to generalize from the results of the study of Lebel and co-workers to adults. A prospective, randomized, placebo-controlled trial of the use of corticosteroids has not been completed in a group of adult patients with meningitis. Because of this, corticosteroids cannot be recommended as routine therapy in adults with bacterial meningitis.

Other agents that reduce inflammation, like superoxide dismutase or nonsteroidal anti-inflammatory drugs, are being studied to further modify the inflammatory response in bacterial meningitis. As further advances are made in the understanding of the pathophysiology of bacterial meningitis, exciting therapeutic alternatives will be developed. The hope is that these therapies will reduce the residual morbidity and mortality of this disease.

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